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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,676	08/02/2002	Bruno Tocque	50146/003002	9433

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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
08/07/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/070,676	TOCQUE ET AL.	
	Examiner	Art Unit	
	HEATHER G. CALAMITA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-105,109-111 and 113-117* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *79-93* is/are allowed.

6)☒ Claim(s) *94-105, 109-111 and 113-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/14/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 14, 2008, has been entered.

Status of Application, Amendments, and/or Claims

2. Claims 79-105, 109-111 and 113-117 are currently pending and under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 94-105, 109-111 and 113-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schena et al. (PNAS, 1996) in view of Komarova et al. (Oncogene, 1998).

With regard to claims 94, Schena et al. teach a method comprising

(a) preparing labeled nucleic acid probes from mammalian cells contacted with a test compound (see p. 10614 under *materials and methods* col. 2 where the nucleic acid probes are derived from Jurkat

cells. Schena et al. teach the cells were either treated with heat (i.e. heat shocked) or not treated (i.e. control) at p. 10615 col. 1 under *Results*).

(b) hybridizing all or part of the nucleic acid probes from step (a) to at least one nucleic acid library capable of detecting the presence of human genes expressed in a cell [see p. 10614 under *Materials and Methods* col. 2 where the nucleic acid probes are derived from Jurkat cells. The library of immobilized nucleic acids is the microarry to which the probes are hybridized. Schena et al. teach the cells were treated with heat (i.e. heat shocked) or not treated (i.e. control) at p. 10615 col. 1 under *Results*].

wherein said nucleic acid library is immobilized on a support and comprises marker nucleic acid molecules specific for all or a portion of one or more differentially spliced regions of one or more human genes expressed in a human cell which is undergoing or has undergone apoptosis and at least one control nucleic acid molecule and (see p. 10614 under *materials and methods* col. 2 where the nucleic acid probes are derived from Jurkat cells. The library of immobilized nucleic acids is the microarry to which the probes are hybridized. Schena et al. teach the cells were either treated with heat (i.e. heat shocked) or not treated (i.e. control) at p. 10615 col. 1 under *Results*. The probes encompass both human genes which are expressed and those which are not. The language of comprising permits the presence of probes for non-expressed genes. The library is made from mRNA which is converted to cDNA. The mRNA from which the cDNA library is made will inherently contain one or more differentially spliced regions of one or more human genes).

(c) detecting hybridization between a plurality of said nucleic acid probes and said marker nucleic acid molecules of said library wherein hybridization indicates the said test compound is toxic (see p. 10615 col. 1 under *Results* Figure 1 and legend where the profile of the heat shocked cells are compared to the cells that were not heat shocked).

With regard to claim 95, Schena et al. teach the nucleic acid probes are mRNAs from said cells contacted with said test compound (see p. 10615 col. 1 under *Results* first full paragraph, where the mRNA from the Jurkat cells treated with heat was isolated, reverse transcribed into labeled cDNA).

With regard to claim 96, Schena et al. teach the nucleic acid probes are, cDNA nucleic acid molecules or cDNA nucleic acid molecule fragments prepared from said cells contacted with said test compound (see p. 10615 col. 1 under *Results* first full paragraph, where the mRNA from the Jurkat cells treated with heat was isolated, reverse transcribed into labeled cDNA).

With regard to claim 97, Schena et al. teach the nucleic acid probes, are amplification products (see p. 10615 col. 1 under *Results* first full paragraph, where the mRNA from the Jurkat cells treated and not treated with heat was isolated, reverse transcribed into labeled cDNA).

With regard to claim 98, Schena et al. teach the nucleic acid probes are labeled by radioactive, fluorescent, enzymatic or colorimetric labels (see p. 10615 col. 1 under *Results* first full paragraph, where the mRNA from the Jurkat cells treated and not treated with heat was isolated, reverse transcribed into labeled cDNA, where the labels are fluorescent, specifically, Cy5 and Fluorescein).

With regard to claim 99, Schena et al. teach the test compound is an individual compound or is present in a mixture of compounds (see p. 10615 col. 1 under *Results* first full paragraph, where the test compound is heat, specifically the cells are heat shocked).

With regard to claim 100, Schena et al. teach the library further comprises nucleic acid molecules specific for genes whose level of expression is modified in a cell (see p. 10614 under *Human cDNA Clones* where the microarray comprises 1046 gene specific cDNAs).

With regard to claim 101, Schena et al. teach the library is prepared by (i) hybridizing a first nucleic acid population from a human cell which is undergoing or has undergone heat shock and a second nucleic acid population from a cell which is not undergoing or has not undergone heat shock and (ii) separating, from the hybrids formed, nucleic acid molecules comprising an unpaired region (see p. 10614

under *materials and methods* col. 2 where the nucleic acid probes are derived from Jurkat cells, which is a cell line derived from human peripheral blood cells. The library of immobilized nucleic acids is the microarry to which the probes are hybridized. Schena et al. teach the cells were either treated with heat (i.e. heat shocked) or not treated (i.e. control) at p. 10615 col. 1 under *Results* and see p. 10615 col. 1 under *Results* Figure 1 and legend where the profile of the heat shocked cells are compared to the cells that were not heat shocked).

With regard to claim 109, Schena et al. teach the cells contacted with said test compound are cell lines (see p. 10615 col. 1 under *Results* first full paragraph, where the mRNA is from Jurkat cells, which is a cell line derived from human peripheral blood cells).

With regard to claim 110, Schena et al. teach the cells contacted with said test compound are primary cultures (see p. 10615 col. 1 under *Results* first full paragraph, where the mRNA was isolated from Jurkat cells).

With regard to claim 111, Schena et al. teach the support is selected from the group consisting of a filter, a membrane, a glass plate or a bio-chip (see p. 10614 col. 2 under *Microarray Preparation* where the support is a microscope slide, specifically the microscope slide is glass).

With regard to claim 113, Schena et al. teach the marker nucleic acid molecules are ordered on the support (see p. 10614 col. 2 under *Microarray Preparation*, where the probes are ordered on the support).

With regard to claims 114 and 115, Schena et al. teach the support comprises between 10 and 50,000 different marker nucleic acid molecules (see p. 10614 col. 2 under *Microarray Preparation*, where there are 1046 nucleic acid molecules on the support).

With regard to claim 116, Schena et al. teach the support consists essentially of marker nucleic acid molecules specific for all or a portion of one or more differentially spliced regions of one or more human genes expressed in a human cell (see p. 10614 under *materials and methods* col. 2 where the

nucleic acid probes are derived from Jurkat cells. The library of immobilized nucleic acids is the microarry to which the probes are hybridized. The probes encompass both human genes which are expressed and those which are not. The library is made from mRNA which is converted to cDNA. The mRNA from which the cDNA library is made will inherently contain one or more differentially spliced regions of one or more human genes).

With regard to claim 117, Schena et al. teach the support comprises marker nucleic acid molecules specific for all or a portion of more than one differentially spliced region of one or more human genes expressed in a human cell (see p. 10614 under *materials and methods* col. 2 where the nucleic acid probes are derived from Jurkat cells. The library of immobilized nucleic acids is the microarry to which the probes are hybridized. The probes encompass both human genes which are expressed and those which are not. The library is made from mRNA which is converted to cDNA. The mRNA from which the cDNA library is made will inherently contain one or more differentially spliced regions of one or more human genes).

Schena et al. do not teach all of the limitations of claims 94-105 and 108-115. Specifically, with regard to claims 94 and 108, Schena et al. do not teach apoptosis.

With regard to claims 94, 116 and 117, Komarova et al. teach apoptosis (see the abstract, where Komarova et al. teach p53 as controlling cell response to apoptosis. Additionally, Komarova et al. teach using DNA array hybridization to study p53-dependent stress response in tissues exposed to radiation as compared to normal tissue).

With regard to claim 102, Komarova et al. teach apoptosis is induced or enhanced in said human cell (see p. 1090 under Results, where Komarova teaches p53 accumulates in cells treated with radiation resulting in apoptosis).

With regard to claims 103 and 104, Komarova et al. teach oncogenes (see abstract, where p53 is the oncogene).

With regard to claim 105, Komarova et al. teach WAF-1 (see p. 1090 Table 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method and microarray as taught by Schena et al. to study apoptosis as an indicator of the toxicity of compounds applied to cells as taught by Komarova et al. in order to have the efficiency of a chip based approach to study gene expression in humans. As noted by Schena, "Microarrays offer a number of advantages over other potential high capacity approaches to expression analysis. The chip based approach enables small hybridization volumes, high array densities, and the used of fluorescent labeling and detection schemes. The use of cDNA clones provides hybridization specificity that is not readily attained with oligonucleotide arrays. The parallel format of the assay provides a simultaneous differential expression readout for greater than 1000 genes (see the paragraph bridging p. 10618 and 10619)." An ordinary practitioner would have been motivated to use the method and microarray as taught by Schena et al. to study apoptosis as an indicator of the toxicity of compounds applied to cells as taught by Komarova et al. in order to have the efficiency of a chip based approach to study gene expression in humans, as the chip based approach enables small hybridization volumes, high array densities, and the used of fluorescent labeling and detection schemes.

Response to Arguments

4. Applicants' arguments with respect to the objections over claims 116 and 117 filed July 14, 2008, were persuasive and the objections are hereby withdrawn. Applicants state claims 108-112 are cancelled, however this is not indicated in the amended claim set. This assertion is presumed to be a typographical error and claims 109-111 were examined on the merits. Applicants' arguments with respect to the 103 (a) rejections over claims 94-105, 109-111 and 113-117, filed July 14, 2008, have been fully considered but they are not persuasive. Applicants argue the amendment distinguishes the claims over Schena and Komarova because these references describe detection of differential gene expression not detecting the

expression of differentially spliced gene products. This argument is not persuasive because as outlined in the rejection above, the nucleic acid molecules of Schena et al. will inherently meet the newly recited limitation of "nucleic acid molecules specific for all or a portion of one or more differentially spliced regions" because the nucleic acid molecules are made from mRNA which is converted to cDNA. The mRNA from which the cDNA library is made will inherently contain one or more differentially spliced regions of one or more human genes. The rejection is therefore maintained.

Allowable Subject Matter

5. Claims 79-93 are allowed. These claims are interpreted as requiring SEQ ID NO: 16 in its entirety, as such SEQ ID NO: 16 is found to be novel and unobvious over the prior art.

Correspondence

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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/Heather G. Calamita, Ph.D./
Examiner, Art Unit 1637